

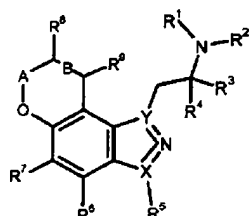
U.S. Patent Application No. 10/722,042
 Amendment dated September 7, 2004
 Reply to Office Action of June 30, 2004

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (currently amended): A compound represented by Formula I:



wherein R^1 and R^2 are independently chosen from hydrogen or an alkyl group;

R^3 and R^4 are independently hydrogen or an alkyl group or;

R^3 and R^4 and the carbon atom to which they are attached form a cycloalkyl ring, or;

R^2 and R^3 together form a saturated $(CH_2)_m$ heterocycle;

R^5 is hydrogen, halogen, or a substituted or unsubstituted alkyl group;

R^6 and R^7 are independently hydrogen, halogen, cyano, an alkylthio, or a substituted or unsubstituted alkyl group;

R^8 and R^9 are independently hydrogen, hydroxyl, a substituted or unsubstituted alkyl group, an alkoxy, $=O$, $NR^{10}R^{11}$, $OC(=O)NR^1R^2$, $OC(=O)C_{1-4}$ alkyl, or an alkylthiol;

R^{10} and R^{11} are independently hydrogen, a substituted or unsubstituted alkyl group, $C(=O)C_{1-4}$ alkyl, $C(=O)OC_{1-4}$ alkyl, or $C(=O)NR^1R^2$ or R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, ~~which optionally~~ or R^{10} and R^{11} together complete a saturated 6-

membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

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A is $(\text{CH}_2)_n$, $\text{C}=\text{O}$, or $\text{CHC}_{1-4}\text{alkyl}$;

B is either a single or a double bond, wherein when B is a double bond, R^8 and R^9 are selected from hydrogen, or a substituted or unsubstituted alkyl group;

$m = 2-4$;

$n = 0-2$;

X and Y are either N or C, wherein X and Y are different; and the dashed bonds denote a suitably appointed single and double bond, and

wherein when $X = \text{C}$ and $A = (\text{CH}_2)_n$ where $n = 0$, then at least one of R^8 or R^9 is a substituted alkyl, $\text{OC}(=\text{O})\text{NR}^1\text{R}^2$, $\text{OC}(=\text{O})\text{C}_{1-4}\text{alkyl}$, an alkylthiol, or $\text{NR}^{10}\text{R}^{11}$ wherein at least one of R^{10} or R^{11} is a substituted alkyl group, $\text{C}(=\text{O})\text{OC}_{1-4}\text{alkyl}$, or $\text{C}(=\text{O})\text{NR}^1\text{R}^2$ or wherein R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, or wherein R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S.

Claim 2 (original): The compound of claim 1, wherein R^2 and R^3 form a saturated $(\text{CH}_2)_m$ heterocycle.

Claim 3 (original): The compound of claim 1, wherein said R^3 and R^4 together form a cyclopropyl ring.

Claim 4 (currently amended): The compound of claim 1, wherein R^1 and R^2 are independently chosen from hydrogen or $\text{C}_{1-4}\text{alkyl}$;

R^3 and R^4 are independently chosen from hydrogen or $\text{C}_{1-4}\text{alkyl}$, or R^2 and R^3 together form a saturated $(\text{CH}_2)_m$ heterocycle;

R^5 is chosen from hydrogen, halogen, or $\text{C}_{1-6}\text{alkyl}$;

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R^6 and R^7 are independently chosen from hydrogen, halogen, cyano, C_{1-4} alkylthio, C_{1-4} alkyl, or C_{1-4} alkyl substituted by halogen;

R^8 and R^9 are chosen from hydrogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, $NR^{10}R^{11}$, or C_{1-6} alkyl substituted with halogen, hydroxyl, or $NR^{10}R^{11}$;

R^{10} and R^{11} are independently chosen from hydrogen or C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, ~~which optionally or~~
 R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an
additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

A is $(CH_2)_n$ or CHC_{1-4} alkyl;

B is either a single or double bond, wherein when B is a double bond, R^8 and R^9 are selected from hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl substituted by halogen, hydroxy, or $NR^{10}R^{11}$;

$m = 3-4$;

$n = 1-2$; and

X and Y are either N or C, wherein X and Y cannot be the same; and

the dashed bonds denote a suitably appointed single and double bond.

Claim 5 (currently amended): The compound of claim 1, wherein R^1 and R^2 are independently chosen from hydrogen or C_{1-4} alkyl;

R^3 is C_{1-2} alkyl, or R^2 and R^3 together are $(CH_2)_3$ to form pyrrolidine;

R^4 is hydrogen;

R^5 is chosen from hydrogen or C_{1-6} alkyl;

R^6 and R^7 are independently chosen from hydrogen, halogen, or C_{1-4} alkyl;

R^8 and R^9 are independently chosen from hydrogen, hydroxyl, C_{1-6} alkoxy, $NR^{10}R^{11}$, or C_{1-6} alkyl substituted with hydroxyl or $NR^{10}R^{11}$;

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R^{10} and R^{11} are independently chosen from hydrogen, C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, ~~which optionally~~ or R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

A is $(CH_2)_n$;

B is a single bond;

$n = 1$;

X is C and Y is N; and

the dashed bonds denote a suitably appointed single and double bond.

Claim 6 (original): The compound of claim 1, wherein said compound is:

1-(2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(S)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-3-methyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(S)-1-Pyrrolidin-2-ylmethyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-5-fluoro-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-dimethylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-methanol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazole-8,9-diol;
1-((S)-2-Aminopropyl)-9-methoxy-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;

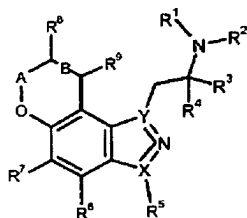
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1-(Pyrrolidin-2-ylmethyl)-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol;
 1-((S)-2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol;
 1-((S)-2-Aminopropyl)-3-methyl-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol; or combinations thereof.

Claim 7 (original): The compound of claim 1, wherein said X is N.

Claim 8 (original): The compound of claim 1, wherein said X is C.

Claim 9 (currently amended): A method of controlling normal or elevated intraocular pressure comprising administering a pharmaceutically effective amount of a composition comprising at least one compound of ~~claim 1~~ represented by the following formula:



wherein R¹ and R² are independently chosen from hydrogen or an alkyl group;

R³ and R⁴ are independently hydrogen or an alkyl group or;

R³ and R⁴ and the carbon atom to which they are attached form a cycloalkyl ring, or;

R² and R³ together form a saturated (CH₂)_m heterocycle;

R⁵ is hydrogen, halogen, or a substituted or unsubstituted alkyl group;

R⁶ and R⁷ are independently hydrogen, halogen, cyano, an alkylthio, or a substituted or unsubstituted alkyl group;

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R⁸ and R⁹ are independently hydrogen, hydroxyl, a substituted or unsubstituted alkyl group, an alkoxy, =O, NR¹⁰R¹¹, OC(=O)NR¹R², OC(=O)C₁₋₄alkyl, or an alkylthiol;

R¹⁰ and R¹¹ are independently hydrogen, a substituted or unsubstituted alkyl group, C(=O)C₁₋₄alkyl, C(=O)OC₁₋₄alkyl, or C(=O)NR¹R² or R¹⁰ and R¹¹ together complete a saturated 5 or 6-membered heterocyclic ring or R¹⁰ and R¹¹ together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S;

A is (CH₂)_n, C=O, or CHC₁₋₄alkyl;

B is either a single or a double bond, wherein when B is a double bond, R⁸ and R⁹ are selected from hydrogen, or a substituted or unsubstituted alkyl group;

m = 2-4;

n = 0-2;

X and Y are either N or C, wherein X and Y are different; and the dashed bonds denote a suitably appointed single and double bond.

Claim 10 (original): The method of claim 9, wherein R² and R³ form a saturated (CH₂)_m heterocycle.

Claim 11 (original): The method of claim 9, wherein said R³ and R⁴ together form a cyclopropyl ring.

Claim 12 (currently amended): The method of claim 9, wherein R¹ and R² are independently chosen from hydrogen or C₁₋₄alkyl;

R³ and R⁴ are independently chosen from hydrogen or C₁₋₄alkyl, or R² and R³ together form a saturated (CH₂)_m heterocycle;

R⁵ is chosen from hydrogen, halogen, or C₁₋₆alkyl;

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R^6 and R^7 are independently chosen from hydrogen, halogen, cyano, C_{1-4} alkylthio, C_{1-4} alkyl, or C_{1-4} alkyl substituted by halogen;

R^8 and R^9 are chosen from hydrogen, hydroxyl, C_{1-6} alkyl, C_{1-6} alkoxy, $NR^{10}R^{11}$, or C_{1-6} alkyl substituted with halogen, hydroxyl, or $NR^{10}R^{11}$;

R^{10} and R^{11} are independently chosen from hydrogen or C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together can complete a saturated 5 or 6-membered heterocyclic ring, ~~which can include~~ or R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring~~;

A is $(CH_2)_n$ or CHC_{1-4} alkyl;

B is either a single or double bond, wherein when B is a double bond, R^8 and R^9 are selected from hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl substituted by halogen, hydroxy, or $NR^{10}R^{11}$;

$m = 3-4$;

$n = 1-2$; and

X and Y are either N or C; wherein X and Y cannot be the same; and

the dashed bonds denote a suitably appointed single and double bond.

Claim 13 (currently amended): The method of claim 9, wherein R^1 and R^2 are independently chosen from hydrogen or C_{1-4} alkyl;

R^3 is C_{1-2} alkyl, or R^2 and R^3 together are $(CH_2)_3$ to form pyrrolidine;

R^4 is hydrogen;

R^5 is chosen from hydrogen or C_{1-6} alkyl;

R^6 and R^7 are independently chosen from hydrogen, halogen, or C_{1-4} alkyl;

R^8 and R^9 are independently chosen from hydrogen, hydroxyl, C_{1-6} alkoxy, $NR^{10}R^{11}$, or C_{1-6} alkyl substituted with hydroxyl or $NR^{10}R^{11}$;

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R^{10} and R^{11} are independently chosen from hydrogen, C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, ~~which optionally or~~ R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

A is $(CH_2)_n$;

B is a single bond;

$n = 1$;

X is C and Y is N; and

the dashed bonds denote a suitably appointed single and double bond.

Claim 14 (original): The method of claim 9, wherein said compound is:

1-(2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(S)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-3-methyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(S)-1-Pyrrolidin-2-ylmethyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-5-fluoro-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-dimethylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-methanol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazole-8,9-diol;
1-((S)-2-Aminopropyl)-9-methoxy-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;

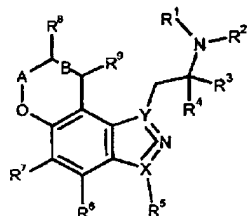
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1-(Pyrrolidin-2-ylmethyl)-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol;
 1-((S)-2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol;
 1-((S)-2-Aminopropyl)-3-methyl-3,7,8,9-tetrahydro-pyrano[3,2-*e*]indazol-8-ol; or combinations thereof.

Claim 15 (original): The method of claim 9, wherein said X is N.

Claim 16 (original): The method of claim 9, wherein said X is C.

Claim 17 (original): A method for the treatment of glaucoma comprising administering a pharmaceutically effective amount of a composition comprising at least one compound of claim 1 represented by the following formula:



wherein R¹ and R² are independently chosen from hydrogen or an alkyl group;

R³ and R⁴ are independently hydrogen or an alkyl group or;

R³ and R⁴ and the carbon atom to which they are attached form a cycloalkyl ring, or;

R² and R³ together form a saturated (CH₂)_m heterocycle;

R⁵ is hydrogen, halogen, or a substituted or unsubstituted alkyl group;

R⁶ and R⁷ are independently hydrogen, halogen, cyano, an alkylthio, or a substituted or unsubstituted alkyl group;

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R⁸ and R⁹ are independently hydrogen, hydroxyl, a substituted or unsubstituted alkyl group, an alkoxy, =O, NR¹⁰R¹¹, OC(=O)NR¹R², OC(=O)C₁₋₄alkyl, or an alkylthiol;

R¹⁰ and R¹¹ are independently hydrogen, a substituted or unsubstituted alkyl group, C(=O)C₁₋₄alkyl, C(=O)OC₁₋₄alkyl, or C(=O)NR¹R² or R¹⁰ and R¹¹ together complete a saturated 5 or 6-membered heterocyclic ring or R¹⁰ and R¹¹ together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S;

A is (CH₂)_n, C=O, or CHC₁₋₄alkyl;

B is either a single or a double bond, wherein when B is a double bond, R⁸ and R⁹ are selected from hydrogen, or a substituted or unsubstituted alkyl group;

m = 2-4;

n = 0-2;

X and Y are either N or C, wherein X and Y are different; and the dashed bonds denote a suitably appointed single and double bond.

Claim 18 (currently amended): The method of claim 17, wherein R¹ and R² are independently chosen from hydrogen or C₁₋₄alkyl;

R³ and R⁴ are independently chosen from hydrogen or C₁₋₄alkyl, or R² and R³ together form a saturated (CH₂)_m heterocycle;

R⁵ is chosen from hydrogen, halogen, or C₁₋₆alkyl;

R⁶ and R⁷ are independently chosen from hydrogen, halogen, cyano, C₁₋₄alkylthio, C₁₋₄alkyl, or C₁₋₄alkyl substituted by halogen;

R⁸ and R⁹ are chosen from hydrogen, hydroxyl, C₁₋₆alkyl, C₁₋₆alkoxy, NR¹⁰R¹¹, or C₁₋₆alkyl substituted with halogen, hydroxyl, or NR¹⁰R¹¹;

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R^{10} and R^{11} are independently chosen from hydrogen or C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together can complete a saturated 5 or 6-membered heterocyclic ring, ~~which can include~~ or R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

A is $(CH_2)_n$ or CHC_{1-4} alkyl;

B is either a single or double bond, wherein when B is a double bond, R^8 and R^9 are selected from hydrogen, C_{1-4} alkyl, or C_{1-4} alkyl substituted by halogen, hydroxy, or $NR^{10}R^{11}$;

$m = 3-4$;

$n = 1-2$; and

X and Y are either N or C, wherein X and Y cannot be the same; and
the dashed bonds denote a suitably appointed single and double bond.

Claim 19 (currently amended): The method of claim 17, wherein R^1 and R^2 are independently chosen from hydrogen or C_{1-4} alkyl;

R^3 is C_{1-2} alkyl, or R^2 and R^3 together are $(CH_2)_3$ to form pyrrolidine;

R^4 is hydrogen;

R^5 is chosen from hydrogen or C_{1-6} alkyl;

R^6 and R^7 are independently chosen from hydrogen, halogen, or C_{1-4} alkyl;

R^8 and R^9 are independently chosen from hydrogen, hydroxyl, C_{1-6} alkoxy, $NR^{10}R^{11}$, or C_{1-6} alkyl substituted with hydroxyl or $NR^{10}R^{11}$;

R^{10} and R^{11} are independently chosen from hydrogen, C_{1-4} alkyl or $C(=O)C_{1-4}$ alkyl or R^{10} and R^{11} together complete a saturated 5 or 6-membered heterocyclic ring, ~~which optionally or~~ R^{10} and R^{11} together complete a saturated 6-membered heterocyclic ring that includes an additional heteroatom selected from N, O, or S ~~when a 6-membered ring;~~

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A is (CH₂)_n;

B is a single bond;

n = 1;

X is C and Y is N; and

the dashed bonds denote a suitably appointed single and double bond.

Claim 20 (original): The method of claim 17, wherein said compound is:

1-(2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(S)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-3-methyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(S)-1-Pyrrolidin-2-ylmethyl-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-((S)-2-Aminopropyl)-5-fluoro-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
(R)-1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-dimethylamine;
[1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-yl]-methanol;
1-((S)-2-Aminopropyl)-1,7,8,9-tetrahydro-pyrano[2,3-g]indazole-8,9-diol;
1-((S)-2-Aminopropyl)-9-methoxy-1,7,8,9-tetrahydro-pyrano[2,3-g]indazol-8-ol;
1-(2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;
1-(Pyrrolidin-2-ylmethyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;
1-((S)-2-Aminopropyl)-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol;
1-((S)-2-Aminopropyl)-3-methyl-3,7,8,9-tetrahydro-pyrano[3,2-e]indazol-8-ol; or combinations thereof.

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Claim 21 (original): A pharmaceutical composition comprising the compound of claim 1 and at least one carrier.

Claim 22 (previously presented): A method to activate or bind to serotonin receptors comprising administering an effective amount of at least one compound of claim 1 to a patient.

Claim 23 (new): The compound of claim 1, wherein $X = C$ and $A = (CH_2)_n$, wherein n is 1 or 2.

Claim 24 (new): The compound of claim 1, wherein $X = C$ and $A = (CH_2)_n$ and $n = 0$ and R^8 or R^9 is a substituted alkyl group.

Claim 25 (new): The compound of claim 1, wherein $X = C$, $A = (CH_2)_n$ and $n = 0$ and B is a single bond.